

# A Theoretical Study on Keto-Enol Tautomerization Involving Simple Carbonyl Derivatives

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## ABSTRACT

The relative stabilities of the keto and enol forms [ $\Delta E^0$  (enol-keto)] and the energy barriers to enolization of the keto forms [ $\Delta E^\ddagger$  (transition state-keto)] for  $\text{CH}_3\text{COR}$  ( $\text{R} = \text{CH}_3, \text{H}, \text{F}, \text{and CN}$ ) and  $\text{CH}_3\text{CHY}$  ( $\text{Y} = \text{CH}_2, \text{NH}, \text{and S}$ ) are investigated theoretically by Hartree-Fock and Möller-Plesset second-order calculations with 6-31G\*\* basis sets. Specific and bulk solvent effects are considered by incorporating one water molecule and applying the self-consistent reaction field (SCRF) method to the reaction system, respectively. The  $\Delta E_{\text{MP2}}^0$  values are all positive, in agreement with the lower stability of the enol form in the gas phase as well as in solution. In contrast to a relatively small effect of specific as well as bulk solvation on  $\Delta E^0$ , there is a large lowering of  $\Delta E^\ddagger$  (by ca. 30 kcal/mol) when solvent effects are accounted for. In general, both  $\Delta E^0$  and  $\Delta E^\ddagger$  are depressed in solution and hence enolization is favored thermodynamically as well as kinetically. The keto form is strongly stabilized by a  $\pi$  donor, whereas the enol isomer is stabilized by a  $\pi$  as well as a  $\sigma$ -acceptor substituent, R. As a result, substituent  $\text{R} = \text{F}$  is the most unfavorable whereas  $\text{R} = \text{CN}$  is the most favorable for the enolization. The water catalyzed enolization in the neutral water proceeds concertedly, but carbon deprotonation is more important than carbonyl-oxygen protonation by water in the rate determining step. © 1997 by John Wiley & Sons, Inc.

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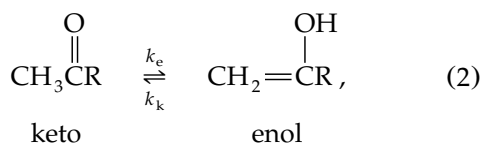
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## Introduction

Recently keto-enol tautomerism involving simple carbonyl derivatives has received considerable interest, largely because of its biochemical importance. Simple enols are usually thermodynamically unstable relative to their carbonyl isomers and hence short-lived so that they are present in very low concentrations as transient intermediates in various organic reactions of aldehydes and ketones.<sup>1</sup> Thus accurate determination of the keto-enol equilibrium constant,  $K_E$ ,

$$K_E = [\text{enol form}]/[\text{keto form}], \quad (1)$$

has been difficult until the recent development of new experimental methods in solution.<sup>2</sup> In the gas phase, however, there are still only limited experimental data available for the relative stabilities of the two forms. The experimental gas-phase energy differences between two forms,  $\Delta E^0$  (enol-keto), for the acetaldehyde-vinyl alcohol [2, R = H in eq. (2)],

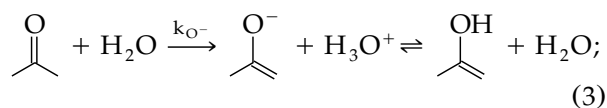


and acetone-propen-2-ol pairs [1, R = CH<sub>3</sub> in eq. (2)] are  $9.9 \pm 2.0$  and  $13.9 \pm 2.0$  kcal/mol,<sup>3b</sup> respectively. For the latter, 11.2 kcal/mol is also reported.<sup>3a</sup> Most of the experimental results reported, however, are  $K_E$  values in water. Keefe and coworkers<sup>4</sup> determined the  $pK_E$  values in water for acetaldehyde (2,  $pK_E = 6.23$ ) and acetone (1,  $pK_E = 8.33$ ) pairs. The corresponding experimental  $\Delta E^0$  values in water are almost identical to those in the gas phase so that no significant differential solvation of one of the tautomers is indicated. On the other hand, the theoretically estimated gas-phase  $\Delta E^0$  values are 11.1 and 14 kcal/mol for the pairs 2 and 1, respectively,<sup>5</sup> which are in good agreement with those for the experimental gas-phase values.

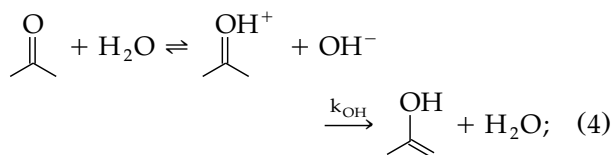
Most of the studies on the mechanisms of the keto-enol tautomerism have been carried out experimentally in solution, especially in the acidic and basic aqueous solution.<sup>2c,6</sup>

The enolization of carbonyl compounds and the ketonization of enols involve two proton transfer steps in solution. According to the principle of

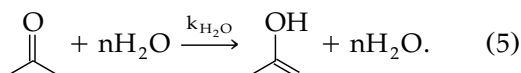
microscopic reversibility, the enolization of simple aldehydes and ketones should occur by the same mechanism as the ketonization of simple enols.<sup>7</sup> In this work, we deal primarily with the enolization mechanism. The enolizations are known to proceed by either acid or base catalysis in the acidic (pH 1–5) or basic (pH 6–12) solution.<sup>6,8</sup> In addition to these catalyzed enolizations by hydronium and hydroxide ions, there is an uncatalyzed portion or water (catalyzed) reaction near the middle of the pH range. The currently accepted mechanisms for the enolization in the neutral pH range of ca. 3–5 are the following three types<sup>6b,8</sup>: rate-determining carbon deprotonation of the keto form by water to hydronium and enolate ions followed by rapid conversion of these products to enol and water, eq. (3);



rapid equilibrium involving ionization of water to give the oxygen-protonated keto form and hydroxide ion followed by rate-determining carbon deprotonation by the hydroxide ion, eq. (4),



and in addition to these stepwise mechanisms in which two proton transfers occur in separate steps, rapid and rate limiting, a concerted mechanism where the two-proton transfer occurs in a single reaction step is also considered, eq. (5). In all of these uncatalyzed neutral reactions, water molecule(s) participate and they are often referred to as *water catalyzed* or *water* reactions.<sup>2c,6b,8</sup>



Kresge and coworkers<sup>2c</sup> commented that there is no experimental evidence as yet available that would allow a choice among these alternatives to be made.

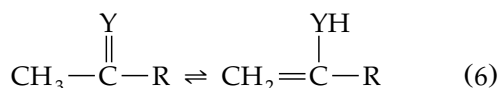
Very few theoretical studies on the mechanism of tautomerization are reported. Noack<sup>9</sup> reported on ab initio studies of the keto-enol tautomerism of several molecules with the STO-3G basis set. Smith et al.<sup>10</sup> studied the potential energy profile involved in the unimolecular rearrangement of

acetaldehyde to vinyl alcohol at the GI level. Their results indicated that the gas-phase barrier height corresponding to the  $k_e$  step in eq. (2) is very high (67.4 kcal/mol) with a four-center hydrogen bridged  $C_1$  symmetry transition state (TS). This means that the enolization process is not only highly endoergic, but also has an extremely high activation barrier in the gas phase.

Ventura et al.<sup>11</sup> investigated different mechanisms (first two mechanisms above) for the conversion of vinyl alcohol to acetaldehyde, both in gas phase and in solution with the STO-3G, 4-31G, and 6-31++G basis sets. They found that the use of the 6-31++G basis set [Hartree-Fock (HF)/6-31++G//HF/4-31G calculation] gives results in qualitative agreement with the experimental facts. To mimic reactions in water solution, they used two methods: effects of specific solvation of reactants where TSs are accounted for by solvation of two water molecules in a chain (water-chain reaction), and bulk solvent effects that are considered using the continuum method of solvation using self-consistent reaction field (SCRF) calculations.<sup>12</sup> The continuum method of solvation was found to be important in recovering a large part of the solvation energy only for the first two mechanisms involving ionic intermediates. However, for the concerted mechanism involving water chains, very little bulk solvent effect was found (for the water-chain mechanism of acetaldehyde enolization the barrier heights were 45.0 and 45.7 kcal/mol, respectively, without and with continuum solvation of water,  $\epsilon = 78.5$ ). Overall when both the specific and bulk solvations are accounted for, the concerted water-chain mechanism (the third mechanism with  $n = 2$ ) was found to be more favorable by ca. 23–24 kcal/mol compared to the stepwise mechanisms (the first two mechanisms with solvation by two water molecules in the chain) involving ionic intermediates. This is, however, at variance with their conclusion<sup>11</sup> that the three mechanisms are equally probable. Their initial state energy should have been that for the solvated reactant by the two water chain; instead they used the initial state energy corresponding to a state consisting of a reactant plus two separated  $H_2O$  molecules.

To extend our understanding of the mechanism, especially on the link between the prohibitively high barrier height involved in the gas-phase enolization predicted by a high level ab initio calculation<sup>10</sup> and the kinetically observable rates of the solution phase tautomerization,<sup>2</sup> we carried out a molecular orbital (MO) theoretical study on the

enolization of some simple carbonyl derivatives, eq. (6), by applying both the bulk and specific solvation effects of water.



	Y	R
1	O	CH <sub>3</sub>
2	O	H
3	O	F
4	O	CN
5	CH <sub>2</sub>	H
6	NH	H
7	S	H

## Computational Methods

Ab initio methods, as implemented in the Gaussian 92<sup>13</sup> suite of programs, were used throughout this work. Structures and energies of the keto and enol forms and the TSs involved in the tautomerization for all the reactants studied [eq. (6)] are optimized at the SCF level with the 6-31G\*\* basis sets<sup>14</sup> and with inclusion of the effects of electron correlation by using Möller-Plesset (MP) perturbation theory<sup>15</sup> at second order, i.e., HF/6-31G\*\*//HF/6-31G\*\* and MP2/6-31G\*\*//MP2/6-31G\*\* by the common notation.<sup>14</sup> These are denoted and referred to as HF and MP2 levels in the text unless otherwise noted. Zero-point energies (unscaled) were evaluated at the MP2/6-31G\*\* level. All stationary point structures were identified as minima or first-order saddle points by calculating harmonic vibrational frequencies at the HF/6-31G\*\* level. To examine bulk solvent effects, the SCRF method<sup>12</sup> was applied with dielectric constants of 78.5 (water) and 20.7 (acetone) by performing single point calculations on the reactants and TSs. We have in addition studied specific solvation effects using one water molecule on each tautomer and TS. The hydrogen-bonded structures and energies were also optimized at the HF and MP2 levels. To examine the effects of additional splitting of valence orbitals and diffuse function, single point calculations were also carried out with the 6-311++G\*\* basis sets<sup>14</sup> at the MP2 level. The kinetic isotope effects were calculated at the MP2/6-31G\*\* level by substituting deuterium

for the migrating H in the water catalyzed tautomerization of the acetaldehyde-vinyl alcohol pair, **2** ( $-\text{CH}_2 \cdots \text{H}(\text{D}) \cdots \text{OH}_2$  and  $\text{DO} \cdots \text{H}(\text{D}) \cdots \text{O}=\text{CH}-$ ).

## Results and Discussion

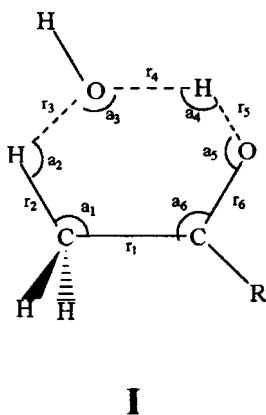
### GEOMETRIES

#### Gas-Phase Reactions

Geometries of the most stable keto forms, TSs, and enol forms involved in the gas-phase reactions are presented in Figure 1 for the five compounds studied, **3**–**7**. The *cis*-enol forms were always more stable than the corresponding anti-forms. The structures of **1** and **2** were reported previously,<sup>10,16</sup> and we have excluded them from Figure 1.

#### Water-Catalyzed Reactions

The MP2 geometries of the monohydrated keto forms, TSs, and enol forms for the four species, **1**–**4**, are presented in Table I. We note that the monohydrated keto form has a structure in which water forms a hydrogen bond toward the carbonyl oxygen, **I**, (e.g., for R = H,  $r_5 = 2.013$  Å).



In addition, the oxygen atom of water is loosely directed to a hydrogen atom of the  $\text{CH}_3$  group (e.g., for R = H,  $r_3 = 2.435$  Å). In the TS, both the  $r_3$  and  $r_5$  bonds are contracted ( $r_3 = 1.189$  and  $r_5 = 1.295$  Å, respectively) and the two proton transfer processes mediated by the water molecule, a proton abstraction from the  $\text{CH}_3$  group and a proton transfer to the carbonyl oxygen, occur concertedly. This can be viewed as a bifunctional concerted catalysis<sup>8,17</sup> by a water molecule. Of

course, in the TS the C — C and C = O bonds are contracted and expanded, respectively, from those of the keto form, both becoming partial double bonds. It is interesting to note that the three O — H bonds in the six-membered cyclic structure of the TS ( $r_3$ ,  $r_4$ , and  $r_5$ ) are within 0.2 Å, e.g.,  $r_3 = 1.189$ ,  $r_4 = 1.148$ , and  $r_5 = 1.295$  Å for R = H. In the enols, the oxygen atom in water is seen to form a hydrogen bond toward the hydroxy hydrogen with the water moving far away from the carbon atoms. This is in contrast to a near cyclic six-member ring structure of the hydrated keto form, which can proceed to the TS with a minimum structural reorganization.

### ENERGETICS

#### Keto-Enol Equilibria in Gas Phase

The optimized energies for the two tautomers and TSs at the HF and MP2 levels are summarized in Tables II and III together with the energy differences,  $\Delta E^0$  (enol-keto) and  $\Delta E^\ddagger$  (TS-keto);  $\Delta E^0$  is the energy difference between the enol and keto forms and  $\Delta E^\ddagger$  is the activation energy for enolization of carbonyl compounds. The positive value of  $\Delta E^0$  indicates that the keto form is the more stable as expected. Surprisingly, the  $\Delta E^0$  values are larger at the MP2 level than corresponding values at the HF level of theory. A similar increase in the  $\Delta E^0$  values is reported for the acetaldehyde-vinyl alcohol pair (**2**) as the electron correlation effects are included, e.g., the  $\Delta E^0$  values are 13.5 and 14.4 kcal/mol at the 6-31G\*\*//6-31G\*\* and MP4SDTQ/6-31G\*\*//6-31G\*\* levels, respectively.<sup>5</sup> In fact the latter value agrees well with our MP2/6-31G\*\*//MP2/6-31G\*\* value. However, this value is reduced further to 11.9 kcal/mol at the MP2/6-311 + + G\*\*//6-31G\*\*<sup>5</sup> and MP2/6-311 + + G\*\*//MP2/6-31G\*\* levels. Comparisons with experimental values require corrections for a temperature change from 0 to 298 K, but contributions of temperature rise are at most a fraction of 1 kcal/mol.<sup>5</sup> Our results at the MP2/6-311 + + G\*\*//MP2/6-31G\*\* level for acetaldehyde-vinyl alcohol (**2**) and acetone-propene-2-ol (**1**) pairs, 11.9 and 13.1 kcal/mol, respectively, are in fact in good agreement with the corresponding gas-phase experimental values of  $9.9 \pm 2.0$  and  $13.9 \pm 2.0$  kcal/mol.<sup>3</sup> Our best gas-phase values are similar to or slightly better than those reported by Apeloig et al. (11 and 14

kcal/mol).<sup>5</sup> In view of these comparisons, improvements of the basis sets by additional splitting of valence orbitals (6-31  $\rightarrow$  6-311) and addition of diffuse functions (+ +) are seen to be more important than the incorporation of higher level electron correlation effects for the more realistic energy differences of the two tautomers.

The energy difference,  $\Delta E^0$ , increases and hence the keto form is relatively more stable than the enol isomer when a  $\pi$  donor is substituted (inductive and resonance substituent constants<sup>18</sup> are  $\sigma_I = -0.05$ ,  $\sigma_R = -0.09$  and  $\sigma_I = 0.51$ ,  $\sigma_R = -0.46$  for R = CH<sub>3</sub> and F, respectively). This increase in the  $\Delta E^0$  value for a  $\pi$ -donor R is in accord with the well-known effects of substituent on the C = O bond:  $\pi$ -donor and  $\sigma$ -acceptor substituents stabilize, whereas  $\pi$  acceptor and  $\sigma$  donor destabilize the C = O bond; and the stabilization ef-

fects of the  $\pi$ -donor substituents are much larger compared to those for the corresponding C = C double bond system.<sup>19</sup> Thus the largest  $\Delta E^0$  value is obtained with R = F, which is a strong  $\sigma$  acceptor as well as a  $\pi$  donor. The relatively low  $\Delta E^0$  value for R = CN ( $\sigma_I = 0.54$ ,  $\sigma_R = 0.09$ ), which is a strong  $\sigma$  acceptor as well as a weak  $\pi$  acceptor, may be related to the greater stabilization of the enol isomer because a vinyl group (C = C) is a stronger  $\sigma$  as well as  $\pi$  donor than the carbonyl group (C = O).<sup>19</sup> This is supported by the dual substituent parameter (DSP) analysis.<sup>20</sup> This type of analysis presented here involved merely four R groups, and hence should be considered to provide a semiquantitative trend only as indicated by relatively large standard deviations for the *a*, *b*, and *c* values; multiple regression analysis of  $\Delta E^0_{MP}$  using the  $\sigma_I$  and  $\sigma_R$  substituent constants

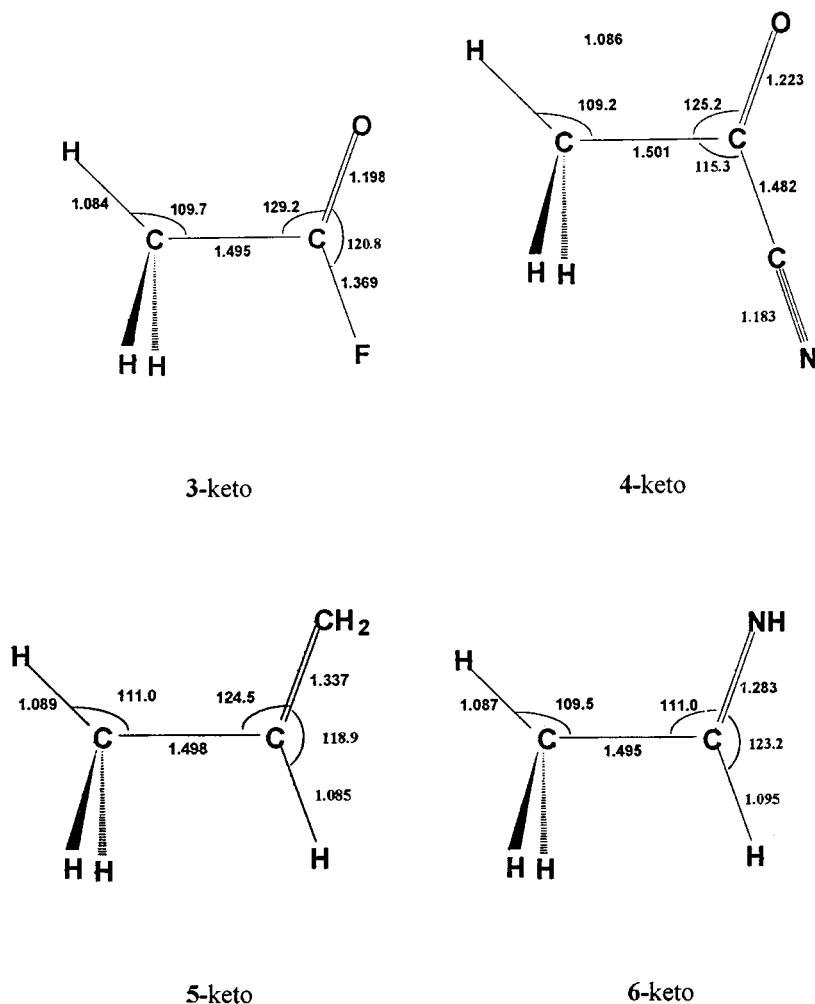


FIGURE 1. Selected geometries of the TS, keto, and enol isomers for compounds 3–7.

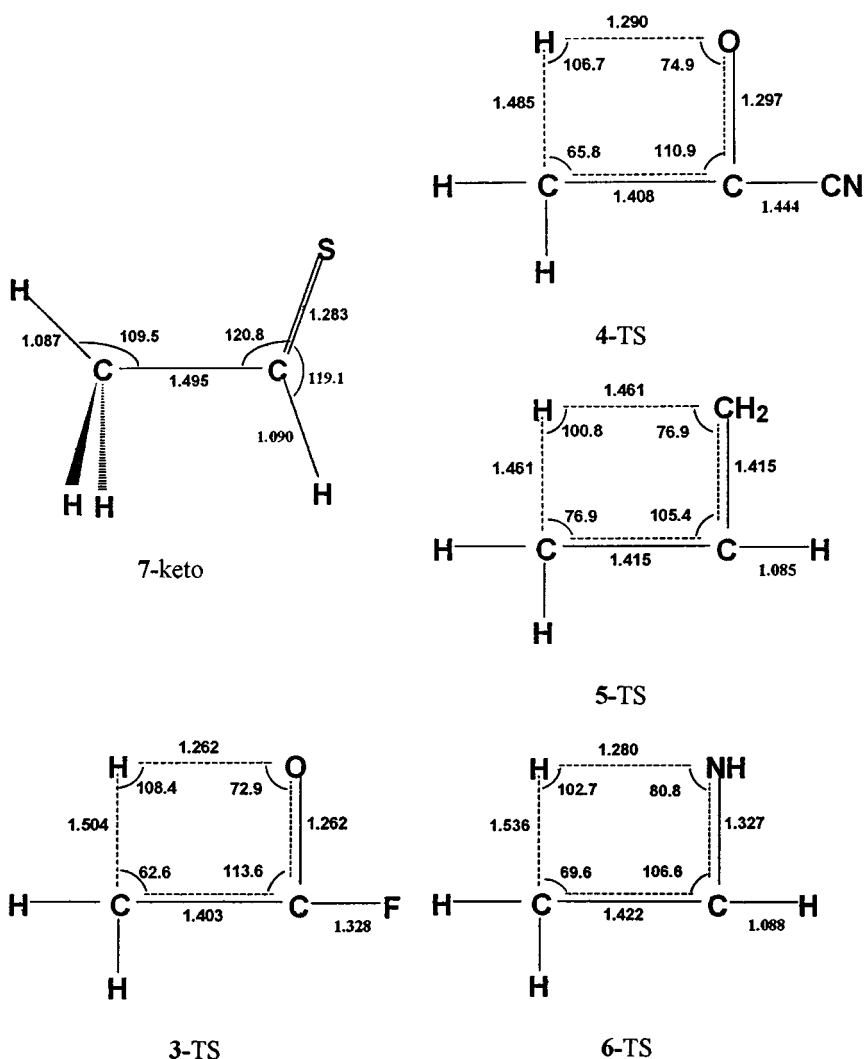


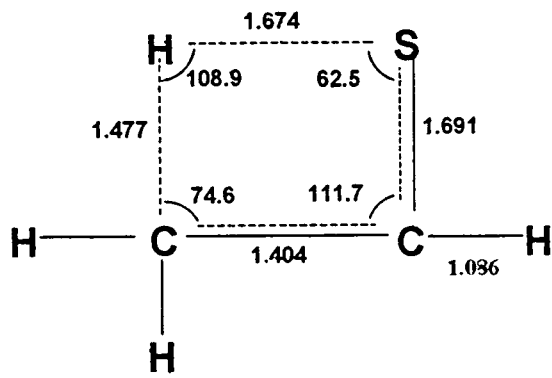
FIGURE 1. (Continued)

for the four R groups in Table II [eq. (7)] gave positive  $a$  and negative  $b$  parameters ( $a = 5.5 \pm 1.7$ ,  $b = -32.5 \pm 2.2$ , and  $c = 17.7 \pm 0.6$  with  $r = 0.998$ ),<sup>21</sup> indicating that a  $\sigma$  acceptor ( $\sigma_I > 0$ ) as well as the  $\pi$  donor ( $\sigma_R < 0$ ) is unfavorable ( $\delta\Delta E^0 > 0$ ) for the stability of the enol tautomer.

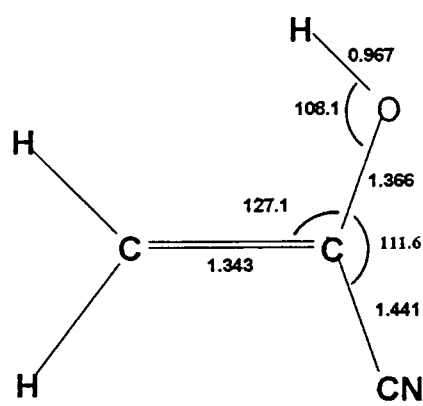
$$\Delta E_{\text{MP}}^0 = a\sigma_I + b\sigma_R + c. \quad (7)$$

However, the very large negative value of  $b$  relative to  $a$  reflects that the enol destabilization effect by a  $\pi$  donor ( $\delta\sigma_R < 0$ ) is much greater than that by a  $\sigma$  acceptor ( $\delta\sigma_I > 0$ ). Moreover the  $\pi$ -resonance effect is further enhanced due to enol stabilization by a  $\pi$ -acceptor ( $\delta\sigma_R > 0$ ) substituent. The depletion of electronic charge from the two car-

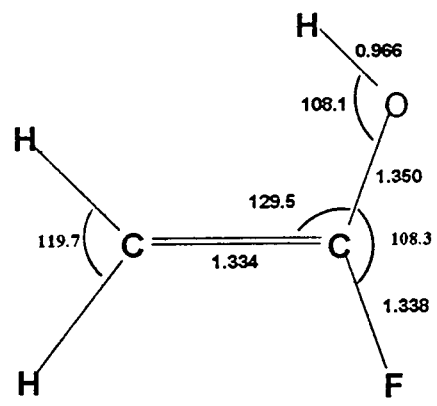
bons in the vinyl group ( $C_1 = C_2$ ) is the largest for R = CN [ $\Delta q(\text{enol-keto}) = 0.580$ ] compared to those for R = CH<sub>3</sub>, H, and F of 0.417, 0.447, and 0.321, respectively (Table IV). This is also reflected in the largest dipole moment of the enol form calculated for R = CN ( $\mu = 5.07$  D). There is in fact a large increase in  $\mu$  [ $\Delta\mu(\text{enol-keto}) = 1.32$ ] for R = CN, in contrast to significant decreases in  $\mu$  ( $\Delta\mu < 0$ ) for other substituents (Table IV). We can therefore conclude that a  $\pi$ -donor substituent (R = CH<sub>3</sub> and F) elevates  $\Delta E^0$  and hence is unfavorable for the enol form due to stabilization of the keto form; whereas the  $\pi$  and  $\sigma$  acceptor (R = CN) depress  $\Delta E^0$  and hence are favorable for the enol form due to stabilization of the enol form.



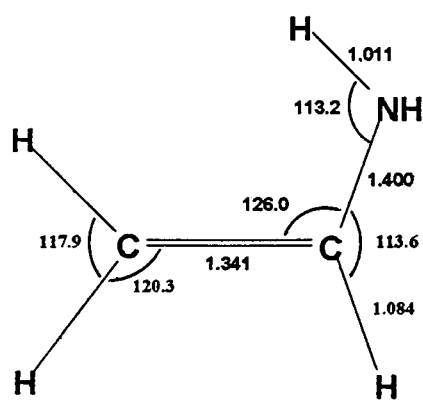
7-TS



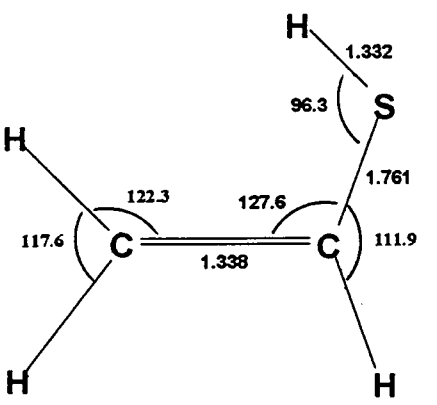
3-enol



4-enol



6-enol



7-enol

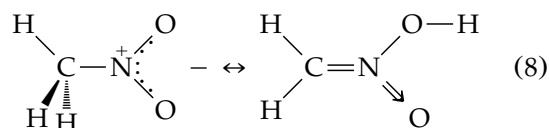
FIGURE 1. (Continued)

**TABLE I.**  
**Structures of Monohydrated Keto, TS, and Enol Forms for Compounds 1 – 4.**

R	$r_1$	$r_2$	$r_3$	$r_4$	$r_5$	$r_6$	$a_1$	$a_2$	$a_3$	$a_4$	$a_5$	$a_6$
CH <sub>3</sub>												
Keto	1.509	1.086	2.435	0.969	1.986	1.232	110.1	142.3	66.6	163.0	114.8	122.2
TS	1.411	1.450	1.199	1.176	1.258	1.289	92.4	144.8	84.0	156.4	102.3	120.9
Enol	1.344	3.490	0.963	1.878	0.976	1.364	92.6	79.1	110.9	178.8	109.4	125.0
H												
Keto	1.498	1.086	2.435	0.968	2.013	1.228	110.4	141.3	68.6	161.2	113.0	124.8
TS	1.404	1.467	1.189	1.148	1.295	1.283	91.1	144.7	85.2	155.2	101.2	123.3
Enol	1.339	4.212	0.963	1.868	0.976	1.361	77.3	43.3	109.9	175.3	108.4	126.9
F												
Keto	1.492	1.084	2.398	0.966	2.081	1.204	109.4	141.3	75.0	153.2	111.2	129.1
TS	1.397	1.558	1.132	1.094	1.297	1.265	89.4	145.2	86.6	155.8	102.7	125.9
Enol	1.336	4.167	0.963	1.795	0.979	1.340	76.2	42.3	112.9	177.8	108.5	129.7
CN												
Keto	1.498	1.086	2.363	0.966	2.085	1.228	109.4	144.0	74.0	153.7	112.7	125.6
TS	1.404	1.509	1.162	1.145	1.385	1.281	90.0	145.2	87.6	153.1	100.2	124.3
Enol	1.346	4.112	0.963	1.805	0.979	1.358	78.7	42.1	113.0	178.9	108.4	127.4

Bond lengths are in angstroms and angles in degrees. Bond length  $r_i$  and angle  $a_i$  are as shown in Structure I.

For comparison, the best reported G1 nitromethane (CH<sub>3</sub>NO<sub>2</sub>)  $\leftrightarrow$  acinitromethane (CH<sub>2</sub> = NO<sub>2</sub>H) energy difference [eq. (8)] of  $\Delta E^0 = 14.1$  kcal/mol in favor of nitromethane<sup>22</sup> is surprisingly similar to the corresponding G1 acetaldehyde  $\leftrightarrow$  vinyl alcohol energy difference of 11.2 kcal/mol.<sup>10</sup>



This could also be related to the stronger  $\pi$ - and  $\sigma$ -donating ability of the C = N bond in the aci-

**TABLE II.**  
**Calculated Electronic Energies, Activation Energies, and Reaction Energies for Direct Tautomerization Processes in Gas Phase.**

R	Basis set	Keto (Hartree)	TS (Hartree)	Enol (Hartree)	$\Delta E^\ddagger$ (kcal / mol)	$\Delta E^0$ (kcal / mol)
1	CH <sub>3</sub>					
	HF <sup>a</sup>	-191.97207	-191.83613	-191.94753	85.31	15.40
	MP <sup>b</sup>	-192.57141	-192.45577	-192.54629	72.56 (75.95) <sup>d</sup>	15.76
2	H					
	MP <sup>c</sup>	-192.65545	-192.54222	-192.63454	69.17	13.12
	HF <sup>a</sup>	-152.92259	-152.78311	-152.90100	87.52	13.55
3	F					
	MP <sup>b</sup>	-153.37847	-153.26104	-153.35559	73.69 (76.96)	14.35
	MP <sup>c</sup>	-153.44951	-153.33701	-153.43050	70.59	11.93
4	CN					
	HF <sup>a</sup>	-251.80349	-251.65122	-251.75716	95.55	29.07
	MP <sup>b</sup>	-252.42206	-252.28882	-252.37183	83.61 (87.15)	31.52
4						
	MP <sup>c</sup>	-252.55962	-252.43122	-252.51366	80.57	28.84
4						
	HF <sup>a</sup>	-244.64714	-244.50318	-244.62741	90.33	12.38
	MP <sup>b</sup>	-245.37605	-245.25722	-245.35439	74.56 (77.98)	13.59
	MP <sup>c</sup>	-245.47958	-245.36536	-245.46171	69.41	11.21

<sup>a</sup>HF/6-31G\*\* // HF/6-31G\*\*.

<sup>b</sup>MP2/6-31G\*\* // MP2/6-31G\*\*.

<sup>c</sup>MP2/6-311 + + G\*\* // MP2/6-31G\*\*.

<sup>d</sup>Corrected for zero-point energy.



**TABLE III.**  
**Calculated Electronic, Activation, and Reaction Energies, for Direct Tautomerization Processes in Gas Phase.**

Y	Keto (Hartree)	TS (Hartree)	Enol (Hartree)	$\Delta E_1^\ddagger$ (kcal / mol)	$\Delta E^0$ (kcal / mol)	$\chi_{YH}^a$
5 CH <sub>2</sub>						
HF	− 117.08161	− 116.91561	− 117.08161	104.17	0	2.56
MP2	− 117.50391	− 117.36324	− 117.50391	88.27	0	
6 NH						
HF	− 133.08422	− 132.94874	− 133.07516	85.02	5.69	3.10
MP2	− 133.53274	− 133.41780	− 133.52199	72.12	6.74	
2 O						
HF	− 152.92259	− 152.78311	− 152.90100	87.52	13.55	3.64
MP2	− 153.37847	− 153.26104	− 153.35559	73.69	14.35	
7 S						
HF	− 475.55834	− 475.43117	− 475.55118	79.80	4.49	2.63
MP2	− 475.96282	− 475.85488	− 475.95081	67.73	7.54	

<sup>a</sup>Group electronegativity.<sup>23</sup>

form (toward a  $\sigma$ -acceptor atom of O) leading to a relatively strong stabilization of the aci-form.

For the substituent F,  $\pi$ -donor effect on the keto form and  $\sigma$ -acceptor effect on the enol form can compete, but the  $\pi$ -donor effect is dominant over the  $\sigma$ -acceptor effect in the gas phase so that  $\Delta E^0$  for R = F is very high.

When the carbonyl oxygen is replaced by Y = CH<sub>2</sub>, NH, or S in CH<sub>3</sub>C(=Y)H, the  $\Delta E^0$  values are much smaller (Table III). Obviously for Y = CH<sub>3</sub>, the tautomers are identical ( $\Delta E^0 = 0$ ); and as the group electronegativities<sup>23</sup> of Y increase,  $\Delta E^0$  also increases. This is in line with a decrease in the stability of the enol-like form and an increase in the stability of the keto-like form as the group electronegativity of Y increases.

We examined the specific solvation effects by one water molecule. In the activation process, this corresponds to a bifunctional water catalyzed tautomerization.<sup>8,17</sup> The results in Table VI indicate that now all the  $\Delta E^0_{MP}$  values are lowered by solvating each tautomer with one water molecule. The relative order for the  $\Delta E^0$  values, R = F > CH<sub>3</sub> > H > CN, remains the same as for those in the uncatalyzed gas-phase processes. Our energy differences,  $\Delta E^0$  (enol-keto), in water simulated by one water hydration at the MP2/6-311 + + G\*\*//MP2/6-31G\*\* for the pairs 2 and 1 (9.9 and 12.7 kcal/mol) are lower than those corresponding to gas-phase values by 2.0 and 0.4

kcal/mol, respectively, and are in good accord with the conclusion drawn by Apeloig et al. that the  $K_{enol}$  (water) are larger [or the  $\Delta E^0$ (enol-keto) values are lower] by 2–3 kcal/mol than in the gas phase.<sup>5</sup>

The multiple regression of  $\Delta E^0_{MP}$  with  $\sigma_I$  and  $\sigma_R$ , eq. (7), ( $a = -1.0 \pm 1.6$ ,  $b = -33.0 \pm 2.1$ , and  $c = 13.0 \pm 0.6$  with  $r = 0.998$ ) shows that  $a$  is now negative or near zero, indicating that the effect of the  $\sigma$ -acceptor substituent is reduced further (ca. 3%) relative to the  $\pi$ -donor effect and is reversed to enol stabilization.

**KETO-ENOL EQUILIBRIA IN SOLUTION**

We carried out the SCRF calculations<sup>12</sup> using the gas-phase geometries of the reactants and TSs. The results are summarized in Table V. Reference to this table reveals that the  $\Delta E^0$  values, on which bulk solvent effects are supposed to be reflected, are slightly greater for R = CH<sub>3</sub>, H, and F, but lower for R = CN compared to those corresponding values in the gas phase (Table II). The results show that the tautomer that has a greater dipole moment (Table IV) is favored in the bulk solvent; for the former three the  $\mu$  values are greater for the keto form and for the latter (R = CN)  $\mu$  is greater for the enol form.

Finally, we examined the bulk solvent effects of water on the water catalyzed processes using the

SCRF method. The data shown in Table VII are our MP2 results incorporating both the specific ( $\text{H}_2\text{O}$ ) and bulk solvent effects. The enol forms were more favorable for  $\text{R} = \text{F}$  and  $\text{CN}$  but there were little changes for  $\text{R} = \text{CH}_3$  and  $\text{H}$  by accounting for the bulk solvent effects (SCRF calculation). The contribution of the  $\sigma$ -acceptor stabilizing effect greatly increased to 31% relative to the  $\pi$ -acceptor resonance effect ( $a = -12.0 \pm 1.7$ ,  $b = -38.2 \pm 2.2$ , and  $c = 12.5 \pm 0.6$  with  $r = 0.998$ ). The decrease in the  $\Delta E^0$  value for  $\text{R} = \text{F}$  was quite significant in the  $\text{H}_2\text{O}$ -catalyzed process ( $31.52 \rightarrow 27.79$  kcal/mol), which was further lowered by accounting for the bulk (water) solvent effect ( $27.79 \rightarrow 24.02$  kcal/mol). Thus for  $\text{R} = \text{F}$  the  $\pi$ -donor effect appears to be much reduced relative to the  $\sigma$ -acceptor effect as a result of solvation by water. The final results of  $\Delta E^0$  in Table VII are converted to the  $\text{p}K_{\text{E}}$  values by assuming there are insignificant entropy and temperature effects.<sup>5</sup> Comparison of our values with corresponding experimental values (in the parentheses in Table VII) indicates that the theoretical  $\text{p}K_{\text{E}}$  values are still 4–5 orders of magnitude greater than the corresponding experimental values in water. This demonstrates that the level of theory applied and the specific solvation by one water molecule were not sufficient and calculations at a higher level with incorporation of many more water molecules are obviously required to simulate the specific solvent effect properly.<sup>24</sup> The effect of solvent, which has a lower dielectric constant ( $\epsilon = 20.7$  for acetone), on  $\Delta E^0$  differs very little from that of water ( $\epsilon = 78.5$ ). This is an indication that bulk solvent (or dielectric constant) has very little effect on the keto-enol equilibria, and hence there may be no significant differential solvation of one of the tautomers when full solvent effects are accounted for as experimentally observed.<sup>5</sup>

### Activation Barriers to Enolization in Gas Phase

The HF and MP2 activation barriers to enolization from the keto forms,  $\Delta E^\ddagger$  (TS-keto) by the gas-phase intramolecular 1,3-hydrogen transfer are given in Tables II and III. The MP2 barriers are lower by 12–16 kcal/mol than the corresponding HF barriers, largely because the electron correlation effects in the TS are greater than those in the keto form. The barrier heights are somewhat elevated when zero-point energy corrections are ap-

plied; however, the relative order of the barrier heights ( $\text{R} = \text{F} > \text{CN} > \text{H} > \text{CH}_3$ ) remains the same. Further lowering of the barriers by 3–5 kcal/mol occurs at the MP2/6-311++G\*\*//MP2/6-31G\*\* level. The DSP analysis<sup>20</sup> by multiple regression of  $\Delta E^\ddagger_{\text{MP}}$  with  $\sigma_{\text{I}}$  and  $\sigma_{\text{R}}$ ,

$$\Delta E^\ddagger_{\text{MP}} = a\sigma_{\text{I}} + b\sigma_{\text{R}} + c, \quad (9)$$

gave relatively poor correlation with  $a = 6.9 \pm 3.0$ ,  $b = -16.1 \pm 4.0$ ,  $c = 72.5 \pm 1.1$ , and  $r = 0.983$ . It is interesting to note that  $a$  is positive, in agreement with the positive value found in the similar regression analysis for  $\Delta E^0$  (*vide supra*) in the gas phase. The positive value of  $a$  indicates that a  $\sigma$  acceptor ( $\sigma_{\text{I}} > 0$ ) as well as a  $\pi$  donor ( $\sigma_{\text{R}} < 0$ ) raises the barrier height to enolization from the keto form, as evidenced by the higher barrier for  $\text{R} = \text{CN}$  than for  $\text{R} = \text{CH}_3$  and  $\text{H}$ , albeit by a small amount. This can be attributed to a relatively early TS along the reaction coordinate. In such a TS, the  $\pi$  bond of  $\text{C} = \text{O}$  has not broken fully and that of  $\text{C} = \text{C}$  has not developed fully so that the  $\sigma$ -donor and  $\pi$ -acceptor effects of  $\text{C} = \text{O}$  with the keto form prevail over the  $\sigma$ - and  $\pi$ -donor effects of  $\text{C} = \text{C}$  in the enol form, leading to a net stabilization of the keto form (*vide supra*). The  $\pi$ -acceptor and  $\sigma$ -donor abilities that stabilize the double bonds are stronger for  $\text{C} = \text{O}$  than  $\text{C} = \text{C}$ .<sup>19</sup> We noted above that in the enol form, the  $\text{C} = \text{C}$  bond donates both  $\pi$  and  $\sigma$  electrons to an acceptor substituent, e.g.,  $\text{R} = \text{CN}$ , to stabilize the enol form.

The TS has a four-membered hydrogen-bond bridged ring structure with  $\text{C}_1$  symmetry as Smith et al.<sup>10</sup> reported for **2**. The TS structures for the gas-phase enolization processes are shown in Figure 1. The migrating hydrogen atom is ca.  $10^\circ$  above the  $\text{C} - \text{C} - \text{O}$  plane (dihedral angle  $D = \angle \text{CCHO} \cong 10^\circ$ ), indicating that it does not proceed by the symmetry allowed 1,3-antarafacial path but takes place in a suprafacial shift. When there is a relatively high lying nonbonding orbital (lone pair) available, the symmetry forbidden suprafacial 1,3-shift is known to become partially allowed due to participation of the lone pair in the TS.<sup>25</sup> The barrier height,  $\Delta E^\ddagger$  (TS-keto), of 73.7 kcal/mol for **2** is higher by 6.3 kcal/mol than that calculated at the G1 level of theory<sup>10</sup>; however, the value is in agreement with the literature value at the same level.<sup>10</sup> For the MP2 values, the correlation be-

tween  $\Delta E^\ddagger_{\text{MP}}$  and  $\Delta E^0_{\text{MP}}$ ,<sup>26</sup>

$$\delta\Delta E^\ddagger = \alpha\delta\Delta E^0 \quad (10)$$

shows a slope of  $\alpha = 0.57(\pm 0.11)$  with  $r = 0.964$ . This suggests that the TS is at approximately half way on the reaction coordinate.<sup>25</sup> Based on the prohibitively high barriers to enolization process ( $\Delta E^\ddagger_{\text{MP}} = 73\text{--}84$  kcal/mol) obtained, we conclude that enolization of the keto forms by direct hydrogen transfer in the gas phase is a highly difficult process, at least at ordinary experimental temperatures.

Barriers to gas-phase intramolecular 1,3-hydrogen transfer reactions (Table III) of etheneb(C = CH<sub>2</sub>), imine (C = NH), and thiocarbonyl (C = S) analogues of acetaldehyde [Y = CH<sub>2</sub>, NH, and S in HC(=Y)CH<sub>3</sub>] are similar to those of the substituted acetaldehydes [RC(=O)CH<sub>3</sub> with R = CH<sub>3</sub>, F, and CN] discussed above (Table II). The MP2 barriers are lower by 12–16 kcal/mol than those corresponding HF barriers. For Y = CH<sub>2</sub> the process is the antarafacial 1,3-sigmatropic hydrogen shift that is the only allowed path. As is well known, the barrier is prohibitively high ( $\Delta E^\ddagger_{\text{MP}} = 88.3$  kcal/mol) due to excessive steric hindrance involved in an antarafacial path.<sup>25</sup> For Y = NH and S, the reactions proceed by a suprafacial process, as discussed above for the substituted acetaldehydes, and the barriers are somewhat lower than that for the antarafacial 1,3-hydrogen transfer of propene.

The activation barriers,  $\Delta E^\ddagger$ , to catalyzed enolization by one water molecule (Table VI) were much lower, especially for the  $\sigma$ -acceptor substituents R = F and CN, than those corresponding values for the gas-phase direct 1,3-hydrogen transfer in Table II. The MP2 barriers were lower by 14–17 kcal/mol than the HF barriers. The MP2 barriers were further lowered by 1–2 kcal/mol at the higher level calculation. Thus monohydration of the keto, TS, and enol forms leads not only to a great lowering of  $\Delta E^0$  but also of  $\Delta E^\ddagger$ ; the enol formation is therefore enhanced kinetically as well as thermodynamically due to participation of one water molecule in the process. The multiple regression of  $\Delta E^\ddagger_{\text{MP}}$  with  $\sigma_I$  and  $\sigma_R$ , eq. (9), now gives a negative value of  $a$  ( $a = -1.7 \pm 1.2$ ,  $b = -13.2 \pm 1.5$ , and  $c = 44.3 \pm 0.4$ , with  $r = 0.993$ ) in contrast to the positive  $a$  obtained for the gas-phase  $\Delta E^\ddagger_{\text{MP}}$  values. Thus in the water catalyzed process a  $\sigma$  as well as a  $\pi$  acceptor (e.g., R = CN)

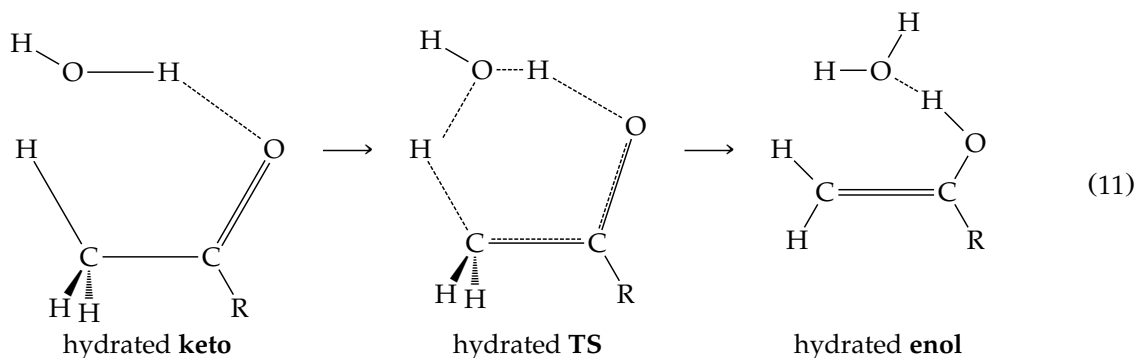
lowers the barrier significantly. This means that  $\sigma$ - and  $\pi$ -donation effects of the C = C bond become than that in the four-membered gas-phase TS structure. This may be attributed to a relatively later TS in the water catalyzed reaction, because in such a TS the  $\sigma$ - and  $\pi$ -donating effects of the C = C bond (to  $\sigma$  and  $\pi$  acceptors, e.g., R = CN) can become dominant over those of the C = O bond.

The large depression (by  $\sim 30$  kcal/mol) of  $\Delta E^\ddagger_{\text{MP}}$  by the catalysis of enolization by one water molecule is in striking contrast to minor changes (0.3–4.2 kcal/mol) in the relative energy difference,  $\Delta E^0_{\text{MP}}$ . The TS structure involving one water has a six-membered hydrogen-bond bridged ring structure relieving large steric strains present in the four-membered ring structure (Fig. 1) for the gas-phase TS. Another factor contributing to the lowering of  $\Delta E^\ddagger$  is that in the water catalyzed reaction, the catalyst water is already in the initial state so that the activation to the TS requires much less reorganization and energy, [eq. (11), *vide supra*]. The stretching of the C — H bond in the TS is ca. 34–44% [ $\%CH^\ddagger = (d^\ddagger_{\text{CH}} - d_{\text{keto}}/d_{\text{keto}}) \times 100$ ], whereas that of the O — H bond of water is less than half of this value, ca. 13–21% ( $\%OH^\ddagger$ ); this is an indication that the carbon deprotonation is much more important than protonation of the carbonyl group in the TS. We calculated kinetic isotope effects for the water catalyzed tautomerization of **2** at the MP2 level. The results indicated that  $k_{\text{H}}/k_{\text{D}}$  is higher for carbon deprotonation [ $k_{\text{H}}/k_{\text{D}} = 3.2$  for  $-\text{CD}_2 \cdots \text{H}(\text{D}) \cdots \text{OH}_2$ ] than for carbonyl-oxygen protonation [ $k_{\text{H}}/k_{\text{D}} = 2.5$  for  $\text{DO} \cdots \text{H}(\text{D}) \cdots \text{O}=\text{CH}-$ ], supporting our conclusion that the carbon deprotonation proceeds somewhat ahead of the carbonyl-oxygen protonation. The C — H isotope effect for the bifunctional catalysis by water for enolization of acetone with AcOH and AcO<sup>−</sup> as catalysts was observed as 5.8 and the solvent deuterium isotope effect was found to be  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 2.0$  for acetone enolization.<sup>17</sup> Our theoretical values compare well with these and others reported for acid and base catalyzed enolization.<sup>27</sup>

Thus even though the two processes are concerted, the enolization mechanism is more like eq. (3) than eq. (4), with the carbon deprotonation as the rate-determining step.

The larger contribution of the  $\sigma$ -acceptor effect of R = CN and F can also be attributed to this

initial hydration of the keto form,



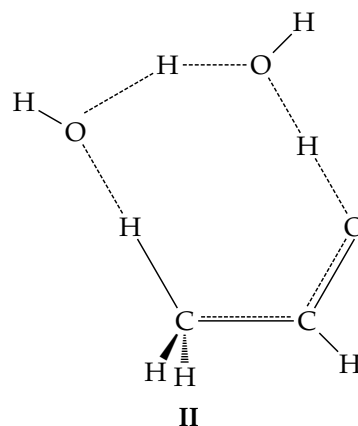
because the double bond character is smaller for  $C=O$  whereas it is greater for  $C=C$ , i.e., the TS is at a much closer position to the product along the reaction coordinate than the corresponding one in the four-membered gas-phase TS. This is also reflected in the same relative order for  $\Delta E^\ddagger$  and  $\Delta E^0$ ,  $R = F > CH_3 > H > CN$ ; for the gas-phase process,  $\Delta E^\ddagger$  was in the relative order  $F > CN > H > CH_3$ , but the order of  $\Delta E^0$  was the same as that for the water catalyzed series.

### Activation Barriers to Enolization in Solution

The SCRf calculations for the enolization of substituted acetaldehydes with  $\epsilon = 78.5$  (water) and  $\epsilon = 20.7$  (acetone) in Table V show a similar elevation ( $\sim 1$  kcal/mol) of the  $\Delta E^\ddagger_{MP}$  values as we found for the SCRf calculations on the  $\Delta E^0_{MP}$  values in Table II. There is a change in the relative order of  $\Delta E^\ddagger$  among the four compounds.

The  $\Delta E^\ddagger_{MP}$  values in Table VII reveal again that inclusion of the bulk solvent effect by the SCRf method leaves little differences in the barriers between those for the two solvents of different dielectric constants as well as those for without bulk solvent effects in Table VI. As already noted above, the  $\Delta E^\ddagger_{MP}$  values for the enols having relatively large dipole moments ( $R = F$  and  $CN$ ) are lowered, but those with relatively low dipole moments ( $R = CH_3$  and  $H$ ) are raised. Our MP2 (MP2/6-31G\*\*//MP2/6-31G\*\*) barrier to enolization of acetaldehyde in water,  $\Delta E^\ddagger_{MP} = 45.6$  kcal/mol, for the bifunctional water (1  $H_2O$ ) catalyzed reaction in neutral water solution ( $\epsilon = 78.5$ ), TS in eq. (11) with  $R = H$ , is surprisingly similar to the barrier calculated using 6-31 + + G basis sets (HF/6-31 + + G//HF/4-31G) for water-chain (2  $H_2O$ ) reaction of acetaldehyde enolization ( $\Delta E^\ddagger =$

45.7 kcal/mol) in solution ( $\epsilon = 80.0$ ), II.



The correlation of  $\Delta E^\ddagger_{MP}$  with  $\Delta E^0_{MP}$ , eq. (10), gives  $\alpha = 0.43 \pm 0.05$  with  $r = 0.985$ . Slightly smaller  $\alpha$  than the gas-phase value ( $\alpha = 0.57$ ) is again due to the initial hydration of the keto forms. Application of eq. (9) results in  $a = -7.2 \pm 1.3$ ,  $b = -16.2 \pm 1.7$ , and  $c = 45.1 \pm 0.5$  with  $r = 0.995$ . The relative contribution of the  $\sigma$ -acceptor effect ( $\sigma_I$ ) to that of the resonance ( $\sigma_R$ ) is relatively high at 69%. This is the cause of depression of  $\Delta E^\ddagger_{MP}$  for the  $\sigma$ -acceptor substituents ( $R = F$  and  $CN$ ) while  $\Delta E^\ddagger_{MP}$  for the other two ( $R = CH_3$  and  $H$ ) are raised, albeit by small amounts.

### Conclusions

The following conclusions can be drawn from our ab initio study reported in this work.

1. In the gas phase,  $\sigma$ -accepting and  $\pi$ -donating groups stabilize the keto form leading

to a larger keto-enol energy difference,  $\delta\Delta E^0(\text{enol-keto}) > 0$ .

- In water, however, it is the enol form that is stabilized primarily by both  $\sigma$  and  $\pi$  acceptors, which results in a decrease in  $\Delta E^0(\text{enol-keto})$  favoring the enol form in water more than in gas phase.
- A similar pattern of substituent effects is followed by the activation barrier to enolization,  $\Delta E^\ddagger(\text{TS-keto})$ : stabilization of the keto form is dominant in the gas phase whereas that of the enol form becomes dominant in water.
- The keto-enol equilibria are little affected by solvents, in contrast to a large decrease in the barrier height in solution.
- The water catalyzed reaction is a concerted process, but carbon deprotonation by water is more important than carbonyl-oxygen protonation by water in the TS.
- The inclusion of diffuse function and further splitting of valence orbitals are more important than incorporation of electron correlation effects (MP2) in the calculation of keto-enol equilibria and the enolization barriers.

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## Supplementary Materials

The following Supplementary Material is available from the authors upon request or via the Internet (see footnote on p. 56):

- Detailed geometries of all structures and energies studied;
- Table IV: MP2 calculated positional charge densities ( $q$  in electronic units) and dipole moment ( $\mu$  in debyes) for the direct tautomerization processes by the NBO method;
- Table V: MP2 calculated energy value of non-catalyzed hydrogen transfer reaction by the SCRF method;
- Table VI: energies for the water catalyzed enolization reactions; and

- Table VII: MP2 (MP2/6-31G\*\*//MP2/6-31G\*\*) calculated energy values for water catalyzed enolizations by the SCRF method.

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